# Do polarized T lymphocytes and T regulatory lymphocytes play a role only in the animal model of atherosclerosis?

**To the Editor** We read a recent review by Jawień[1] with great interest. It is a significant voice in the field of atherosclerosis. Being excellent, this paper raises a few concerns for human studies in comparison with the animal model. However, a few opinions presented in the review, namely, that "humans lack Th1 and Th2 polarization that is observed in mice" and that "FoxP3 expression is a useful marker of $T_{reg}$ cells in mice, but not in humans", need some commentary.

The first point to be discussed is the polarization of T-helper (Th) 1 and Th2 lymphocytes in humans. Different infectious agents evoke an adequate adaptive immune response that clears an infection. The immune system adapts itself to the specific conditions of infection by producing different profiles of cytokines, which drive naïve CD4 T cells to differentiate into appropriate effector Th subset: Th1 or Th2. This step is critical for effective immune response because it determines its path – cellular or humoral. From these 2 subsets of T cells, Th1 are the main contributors to atherosclerosis and their characteristic cytokine, interferon-γ (IFN-γ), is observed in human plaques. The abundance of IFN-γ has not only dramatic consequences because of the activation of macrophages, but also causes decreased collagen fiber formation, higher expression of major histocompatibility complex class II, enhanced protease and chemokine secretion, upregulation of adhesion molecules, and induction of proinflammatory cytokines. Interleukin 4, the cytokine of Th2 lineage, is in fact rarely observed in human plaques, which, in line with the available data, proves the crucial role of Th1 subset in the pathogenesis of atherosclerosis, probably also in humans. The presence of Th1/Th2 polarized lymphocytes in humans has been confirmed in pregnancy and numerous clinical conditions, e.g., allergic disorders.[2-4]

Second issue that needs to be clarified is forkhead box 3 (FoxP3) as a marker of human regulatory T ($T_{reg}$) lymphocytes. The characterization of $T_{reg}$ cells by the expression of FoxP3 protein, initially in mice and subsequently in humans, was a critical step in the elucidation of their biology. Mutation of the *FoxP3* gene in mice was originally connected with X-linked recessive inflammatory disease. Further studies in humans demonstrated that mutation in human *FoxP3* gene is responsible for X-linked immunodeficiency syndrome (also known as immune dysregulation, polyendocrinopathy, enteropathy, X-linked syndrome). FoxP3 belongs to the family of transcription factors and is the main controller during $T_{reg}$-cell development, and a hallmark of active $T_{reg}$ cells. Human $T_{reg}$ cells were first characterized by the presence of CD4 and CD25 molecules, the same as in the mice model. In fact, the *FoxP3* gene was described as a master gene controlling the development of $T_{reg}$ cells in mice. Subsequently, it was shown that the human version of FoxP3 protein is also crucial for the function of human $T_{reg}$ cells. Furthermore, FoxP3 is exclusively expressed by $CD25^+CD4^+$ $T_{reg}$ cells, while other T cells, B cells, and natural killer cells do not express it. $T_{reg}$ cells are commonly classified as "natural" and "induced". A natural subset, which develops and emigrates from the thymus, is $CD4^+CD25^+$. Induced $T_{reg}$ cells are also characterized as $CD4^+CD25^+$, but they acquire CD25 (α chain of the interleukin 2 receptor) outside the thymus.

There have been several reports describing the role of $T_{reg}$ cells in several pathologies both in humans and in the murine model.[5] It is crucial to be aware of the pivotal differences but also similarities between animal models and humans.

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